Abstract

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Regionally selective alterations in local cerebral glucose utilization evoked by charybdotoxin, a blocker of central voltage-activated K^+-channels

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Abstract

The quantitative [^{14}C]-2-deoxyglucose autoradiographic technique was employed to investigate the effect of charybdotoxin, a blocker of certain voltage-activated K^+ channels, on functional activity, as reflected by changes in local rates of cerebral glucose utilization in rat brain. Intracerebroventricular administration of charybdotoxin, at doses below those producing seizure activity, produced a heterogeneous effect on glucose utilization throughout the brain. Out of the 75 brain regions investigated, 24 displayed alterations in glucose utilization. The majority of these changes were observed with the intermediate dose of charybdotoxin administered (12.5 pmol), with the lower (6.25 pmol) and higher (25 pmol) doses of charybdotoxin producing a much more restricted pattern of change in glucose utilization. In brain regions which displayed alterations in glucose at all doses of charybdotoxin administered, no dose dependency in terms of the magnitude of change was observed. The 21 brain regions which displayed altered functional activity after administration of 12.5 pmol charybdotoxin were predominantly limited to the hippocampus, limbic and motor structures. In particular, glucose utilization was altered within three pathways implicated within learning and memory processes, the septohippocampal pathway, Schaffer collaterals within the hippocampus and the Papez circuit. The nigrostriatal pathway also displayed altered local cerebral glucose utilization. These data indicate that charybdotoxin produces alterations in functional activity within selected pathways in the brain. Furthermore the results raise the possibility that manipulation of particular subtypes of Kv1 channels in the hippocampus and related structures may be a means of altering cognitive processes without causing global changes in neural activity throughout the brain.

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Paper

Developmental Seizure Susceptibility of Kv1.1 Potassium Channel Knockout Mice

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Abstract

Potassium channels play a critical role in limiting neuronal excitability. Mutations in certain voltage-gated potassium channels have been associated with hyperexcitable phenotypes in both humans and animals. However, only recently have mutations in potassium channel genes (i.e. *KCNQ2* and *KCNQ3*) been discovered in a human

epilepsy, benign familial neonatal convulsions. Recently, it has been reported that mice lacking the voltage-gated Shaker-like potassium channel Kv1.1 α-subunit develop recurrent spontaneous seizures early in postnatal development. The clinical relevance of the Kv1.1 knockout mouse has been underscored by a recent report of epilepsy occurring in a family affected by mutations in the *KCNA1* locus (the human homologue of Kv1.1) which typically cause episodic ataxia and myokymia. Here we summarize preliminary studies characterizing the developmental changes in seizure susceptibility and neuronal activation in the three genotypes of Kv1.1 mice (-/-, +/-, +/+). Using behavioral and immediate-early gene indicators of regional brain excitability, we have found that a seizure-sensitive predisposition exists in Kv1.1 -/- animals at a very young age (P10), before either spontaneous seizure activity or changes in c-fos mRNA expression can be demonstrated. Kv1.1 +/- mice, although behaviorally indistinguishable from wild types, also have an increased susceptibility to seizures at a similar early age. The Kv1.1 knockout mouse possesses many features desirable in a developmental animal epilepsy model and represents a clinically relevant model of early-onset epilepsies.

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